REMARKS

The applicant expresses appreciation to the Examiner for consideration of the subject patent application. This amendment is in response to the Office Action mailed April 21, 2005. Claims 1-23 were rejected.

Claims 1-23 were originally presented. Claims 1 and 9 have been amended. Support of the amendments can be found throughout the application. i.e. page 4, lines 1-10 and Example 5.

A new IDS and PTO-1449 form are attached as requested by the Examiner.

Claim Rejections - 35 U.S.C. § 103

Claims 1-10 and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Cha et al. (5,702,717) in view of EP 0092918(Churchill).

The burden is on the Examiner to establish a case of *prima facie* obviousness. *In re Fine*, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). In order to do this by combining references, the prior art must provide some reason or motivation to make the claimed compositions, *In re Dillon*, 16 U.S.P.Q.2d 1897, 1901 (Fed. Cir. 1990) (en banc). When making a rejection under 35 U.S.C. § 103 there are three fundamental areas the Examiner is required, under 37 C.F.R. § 1.106 and MPEP § 706.02, to cover. First, the rejection should set forth the differences between the claims and the prior art. Second, the proposed modification of the applied references necessary to arrive at the claimed subject matter should be clearly stated. Third, there must be an explanation as to why such proposed modifications would be obvious.

In the rejections entered by the Examiner under § 103, there is a common flaw which cannot be resolved simply by the Examiner making an allegation that "it would be obvious". There must be some reason, suggestion or motivation in the art cited to combine the references in the manner stated by the Examiner. Were it not for first having read the Applicants' disclosure and then by hindsight application attempting to piece together portions of each reference rather than considering each reference for what it teaches as a whole, it is not believed a rejection would have been entered. With the above background in mind the rejection under 35 U.S.C. § 103 will be discussed.

The present invention provides drug delivery systems that are biodegradable, exhibit improved reverse thermal gelation behavior, and provide improved drug release characteristics. The drug delivery systems of the present invention are biodegradable polymeric systems possessing reverse thermal gelation properties comprising a mixture of at least a Component I triblock copolymer and a Component II triblock copolymer. The triblock copolymers of the present invention comprise biodegradable polyester A-polymer blocks and polyethylene glycol B-polymer blocks, wherein the B-polymer block of said Component I triblock copolymer has an average molecular weight of 900 to 2000 Daltons and the B-polymer block of said Component II triblock copolymer has an average molecular weight of 600 to 2000 Daltons. The Component I triblock copolymer has an average molecular weight of between 2500 to 8000 Daltons and the component II triblock copolymer has an average molecular weight of between 800-7200 Daltons. As shown in the amended claims 1 and 9, the biodegradable polymeric system of the present invention is water soluble and contains 51 to 83 % by weight of hydrophobic A polymer blocks and 17 to 49 % by weight of hydrophilic B polymer blocks and wherein an aqueous solution of said Component I triblock copolymer has a lower gelation temperature than an aqueous solution of said Component II triblock copolymer.

In Cha, the block copolymer contains less than 50% by weight of a hydrophobic A polymer block and more then 50% by weight of a hydrophilic B polymer block(PEG)(Claim 1). Also in col.8, lines 32-35, Cha discloses that "biodegradable block copolymers possessing thermally reversible gelation properties are prepared wherein the hydrophilic B block makes up about 50-85% by weight of the copolymer and the hydrophobic A block makes up about 15 to 50% by weight of the copolymer." In contrast, the biodegradable polymeric system of the present invention comprises 51 to 83% by weight of a hydrophobic A polymer block and 17 to 49 % by weight of a hydrophilic B polymer block(PEG)(amended Claim 1).

This disclosure by Cha is in conformity with what is commonly known by those skilled in the art regarding solubility of triblock polymers. Specifically, it is generally taught that any polymer having a hydrophobic content in excess of 50% by weight is substantially insoluble in water and can only be made appreciably soluble in aqueous systems, if at all, when a certain amount of an organic cosolvent has been added.

Conversely, the present invention is based on the discovery that a **mixture** of block copolymers, where the A-blocks are a relatively hydrophobic and the B-block is a relatively hydrophilic polyethylene glycol (PEG), having a hydrophobic content of between about 51 - 83% by weight exhibit water solubility at low temperatures and undergo reversible thermal gelation at mammalian physiological body temperatures. With such high hydrophobic contents (51 - 83%), it is unexpected that such block copolymers would be water soluble.

Furthermore, it was an unexpected discovery that a **mixture** of block copolymers with such a large proportion of hydrophobic component would be water soluble below normal room temperature such as refrigerator temperatures (5°C). In addition, despite the fact that hydrophobic polymer block(s) are the major component (51- 83%), the water soluble mixture of block copolymers of the present invention aid in an additional increase in drug solubility when combined in an aqueous phase of the block copolymers. Finally, as the Examiner acknowledges, Cha does not teach "a mixture of two different copolymers."

Churchill discloses amphipathic copolymers which are capable of absorbing water to form a hydrogel when placed in water or an aqueous physiological-type environment in an animal body. Churchill does not teach a block copolymer system having reverse thermal gelation properties. In addition, it was not known in the art prior to the present invention that using a higher hydrophobic polymer content for the A-blocks would result in a water soluble triblock polymer mixture that is a liquid at lower temperatures and gels at higher physiological temperatures. In fact, both of these properties are counterintuitive. Using more of a hydrophobic polymer block provides a triblock polymer that is unexpectedly water soluble.

Furthermore, it was unexpectedly found that these ABA-block tripolymers would gel at higher temperatures and exist in a liquid state at lower temperatures. There is no indication that the Churchill block copolymers are soluble in aqueous solutions at any temperature without the use of organic solvents, nor is there any indication that these drug/polymers can be administered as a solution. Although Churchill discloses blending different copolymers to obtain varying duration release rates, no motivation is provided to blend various block copolymers to obtain a water soluble triblock polymer mixture that is a liquid at lower temperatures and gels at higher physiological temperatures, as claimed in the present invention.

In summary, first, nothing in Cha or Churchill suggests a block copolymer having less than 50% of a hydrophilic component. The present invention requires less than 50% hydrophilic content, whereas, the cited reference requires greater than 50% of a hydrophilic component. Second, the reverse thermal gelation properties discussed previously are not present in the Churchill disclosure and are not realized by Churchill. Furthermore, the presently claimed block copolymers have reversal thermal gelation temperatures lower than the block copolymers disclosed in Cha due to different ratios of hydrophobic and hydrophilic blocks within the block copolymer mixture. Third, the fact that the present invention includes more of the hydrophobic component, and yet, the mixture is water soluble is certainly unexpected. Furthermore, no motivation is provided to combine Churchill, which teaches blending copolymers to regulate the release rate and duration, with Cha to obtain a system with improved reverse thermal gelation properties as claimed in the present invention. Nothing in Churchill teaches or suggest blending two tri-block copolymers wherein an aqueous solution of said Component I triblock copolymer has a lower gelation temperature than an aqueous solution of said Component II triblock copolymer. Finally, even combining the cited references still does not teach or suggest all of the elements of the amended claims 1 and 9. Since claims 2-8 and 10-23 are dependent claims based on claims 1 and 10, they are patentable if claims 1 and 9 are patentable based on the above reasons.

Therefore, in view of the above, it is believed that the Examiner has failed to establish a case of *prima facie* obviousness. In other words, one of ordinary skill in the art when combining all the knowledge and methods disclosed in the cited prior art, at the time of the invention was made, would not come up with the triblock copolymer mixtures as claimed in the present invention. Thus, the Examiner is respectfully requested to withdraw the rejections of Claims 1-23 as being unpatentable over the cited references.

Claims 1-23 are rejected under 35 U.S.C. § 103 as being unpatentable over Cha et al. (5,702,717) in view of Shah et al.(6,451,346). Cha has been discussed above and thus is not repeated here. Shah relates to AB diblock or ABA triblock copolymers with functionalized end groups for controlled delivery. Particularly, the carboxy terminated end groups impart differences in release rates after day 5. In addition, Shah's polymers swelling properties are also

related to the terminal end groups. Shah requires ionic groups to affect the rate of degradation, de-gelation, and rate of clearance(Column 6 line 1). Also, salts, sugars, and surfactants are added to alter the LCST(Column 7 line 1). The polymers of Shah are pH sensitive because they lose their thermal gelation properties in an environment with a pH value above 5.0. In contrast, the polymers of the present invention become gels at the proper temperature and maintain their gel status regardless of the pH value of the environment, and they don't gradually swell as the polymer erodes (Figure 4). In addition, since Shah's polymers respond to pH, which varies depending on the site of injection, they cannot form gels at a neutral pH. De-gelation in Shah occurs when the depot approaches the normal body pH. Therefore, the polymers of the present invention are less dependent on the environment, while the properties of the ionic system of Shah are dependent on where it is located. The gelation properties of the block copolymers of the present invention allow us to formulate them with compounds at a wide range of pH values, while Shah's system would only be applicable below a pH of 5 for which the system forms a gel. Therefore, use of Shah's system would not be feasible when the polymer is used to deliver a compound whose solubility requires a pH above 5. Therefore, the block copolymers of the present invention are patentably distinct from the polymers disclosed in Shah. Furthermore, no motivation is provided to blend various block copolymers to obtain a water soluble triblock polymer mixture that is a liquid at lower temperatures and gels at higher physiological temperatures, even when the pH value is above 5, as claimed in the present invention. Therefore, that the Examiner has failed to established a case of *prima facie* obviousness. The examiner is respectfully requested to withdraw the rejections of Claims 1-23 as being unpatentable over the cited references.

Double Patenting

Claims 1-8 and 18-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/186462(hereafter referred as "'462"). The applicant respectfully traverses because the subject matter of the present invention is patentably distinct from and is not an obvious

modification of the subject matter disclosed in the copending Application No. 10/186462. Application '462 relates to 1) one or more biodegradable block copolymer drug carriers comprising A-B, A-B-A or B-A-B block copolymers having a total weight average molecular weight of 1000 to 100,000 Daltons, wherein the A block is a biodegradable polyester or poly(ortho ester) and the B block is polyethylene glycol(PEG), and the weight percentage of the A block is between 20% to 99% and the weight percentage of the B block is between 1% to 80%; and 2) a liquid polyethylene glycol(PEG), a PEG derivative, or a mixture of PEG and a PEG derivative, said PEG or PEG derivative having a molecular weight of 150 to 1100 Daltons; wherein the biodegradable block copolymeric drug carrier is soluble in the liquid PEG, PEG derivatives, or mixtures of PEG and PEG derivatives.

In contrast, the polymeric systems as claimed in Claims 1-8 and 18-19, have reverse thermal gelation properties, and are comprised of amphiphilic, biodegradable triblock copolymers that form thermal gels and have a high weight percentage (at least 50 weight percent) of hydrophobic blocks. The resulting composition of triblock copolymers and water results in the drug being dissolved by the action of the triblock copolymers thereby enhancing efficiency and facilitating administration of a uniform and accurate dose which may then, in many cases, enhance the therapeutic effects of the drug. Controlling the molecular weights, compositions, and relative ratios of the hydrophilic and hydrophobic blocks may optimize such solubilizing effects. The essence of '462 lies in the element of "a water soluble, low molecular weight polyethylene glycol (PEG), PEG derivatives, or mixtures of PEG and PEG derivatives" and their use for facilitating the reconstitution of biodegradable block copolymeric drug carriers in a hydrophilic environment. However, nothing in '462 teaches a blend of various block copolymers to obtain a water soluble triblock polymer mixture that is a liquid at lower temperatures and gels at higher physiological temperatures. In addition, since the block copolymers of the present invention have reverse thermal gelation properties, they are mainly used to make drug solutions for administration at a temperature lower than body temperature. The drug solution gels as its

temperature rises and forms a drug containing gel/depot which provides for sustained drug delivery. However, the system claimed in '462 can be reconstituted quickly and form homogeneous, free-flowing solutions or uniform colloidal systems in water when present from 1% up to 40% by weight. Reconstitution is the process of mixing an agent to be reconstituted with a solvent, which in the case of pharmaceuticals is usually aqueous. After reconstitution the mixture may exist in the final physical state as either a true solution or as a uniform colloidal or suspension system. The time course for achieving a final physical state of the mixture should be rapid and facile. The '462 invention relates to compositions that enable rapid reconstitution of block copolymeric drug carriers to the final physical state as either a true solution or as a uniform colloidal system. Therefore, even though the reconstitution agent of the '462 can be used with the block copolymers of the present invention, one skilled in the art would not derive the present invention based on the disclosure of '462. Therefore, subject matter disclosed in the present invention is patentably distinct from the subject matter disclosed in the '462 and the provisional double patenting rejection based on '462 should be withdrawn.

Claims 1-8 and 18-19 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/167768(hereafter referred as "'768"). Since copending Application No. 10/186462 is a CIP based on copending Application No. 10/167768, the arguments above should be also applicable to address this rejection. Therefore, the subject matter disclosed in the present invention is patentably distinct from the subject matter disclosed in the '768 and the provisional double patenting rejection based on '768 should be withdrawn.

Claims 1-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of copending Application No. 10/734740(hereafter referred as "'740") in view of Shah. The applicant respectfully traverses because the subject matter of the present invention is patentably distinct from and is not an obvious modification of the subject matter disclosed in '740 in view of Shah.

The differences between the present invention and Shah have been discussed in relation to the previous 103 rejection and they are also applicable here. '740 relates to water soluble, low molecular weight, biodegradable block copolymers having a high weight percentage (at least 50

percent) of hydrophobic block(s), and their use for solubilizing a hydrophobic drug in a hydrophilic environment. The system is based on the discovery that only a select subset of such block copolymers exist as high viscosity liquids in neat form and can form solutions in water at temperatures above body temperature for parenteral and particularly for intravenous (I.V.) delivery and can be used as solubilizing agents for drugs which are substantially insoluble in water, or as solubilizing agents for drugs that require enhancement of their water solubility. However, the block copolymers disclosed in the present invention are mixtures of block copolymers which possess reverse thermal gelation properties wherein the sol/gel transition temperature is generally lower than body temperature which is not suitable for I.V. delivery purposes. In addition, since the block copolymers of the present invention have reverse thermal gelation properties, they are mainly used to make drug solutions for administration at a temperature lower than body temperature. The drug solution gels as its temperature rises and forms a drug containing gel/depot which provides for sustained drug delivery. However, the system claimed in '740 exists as a high viscosity liquid in neat form and can form solutions in water at temperatures above body temperature for parenteral and particularly for intravenous (I.V.) delivery. The drug solutions of the '740 polymers do not have reverse gelation properties and are mainly used as solubilizing agents for drugs which are substantially insoluble in water, or as solubilizing agents for drugs that require enhancement of water solubility. Therefore, the subject matter disclosed in the present invention is patentably distinct from the subject matter disclosed in '740 in view of Shah and the provisional double patenting rejection based on '740 in view of Shah should be withdrawn.

Claims 1-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 6,592,899(hereafter referred as "'899") in view of Shah. The applicant respectfully traverses because the subject matter of the present invention is patentably distinct from and they are not an obvious modification of the subject matter disclosed in '899 in view of Shah.

The differences between the present invention and Shah have been discussed in relation to the previous 103 rejection and they are also applicable here. '899 relates to polymeric compositions having improved capability of solubilizing a hydrophobic drug in a hydrophilic

environment to form a solution. The composition comprises a biodegradable polyester oligomer and water soluble, low molecular weight, biodegradable block copolymers having a high weight percentage (at least 50 percent) of hydrophobic block(s), and their use for solubilizing a hydrophobic drug in a hydrophilic environment. The system is based on the discovery that only a select subset of such block copolymers exist as high viscosity liquids in neat form and can form solutions in water at temperatures above body temperature for parenteral and particularly for intravenous (I.V.) delivery and can be used as solubilizing agents for drugs which are substantially insoluble in water, or as solubilizing agents for drugs that require enhancement of their water solubility.

However, the block copolymers disclosed in the present invention are mixtures of block copolymers which possess reverse thermal gelation properties wherein the sol/gel transition temperature is generally lower than body temperature which is not suitable for I.V. delivery purposes. In addition, since the block copolymers of the present invention have reverse thermal gelation properties, they are mainly used to make drug solutions for administration at a temperature lower than body temperature. The drug solution gels as its temperature rises and forms a drug containing gel/depot which provides for sustained drug delivery. However, the system claimed in '899 exists as a high viscosity liquid in neat form and can form solutions in water at temperatures above body temperature for parenteral and particularly for intravenous (I.V.) delivery. The drug solutions of the '899 polymers do not have reverse gelation properties and are mainly used as solubilizing agents for drugs which are substantially insoluble in water, or as solubilizing agents for drugs that require enhancement of water solubility. Furthermore, the '899 composition contains a biodegradable polyester oligomer, which teaches away from the present invention because adding the oligomer will impair the reverse thermal gelation properties of the present invention. Therefore, the subject matter disclosed in the present invention is patentably distinct from the subject matter disclosed in '899 in view of Shah and the provisional double patenting rejection based on '899 in view of Shah should be withdrawn.

Claims 1-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 09/827100(which has been allowed)(hereafter referred as "'100") in view of Shah. Since the present application is a

divisional of the '100, the present application will have the same patent term as the '100 if it is allowed. Although a terminal disclaimer can be filed to overcome an obvious type double patenting rejection, it is not necessary in the present case because the present application is a divisional application of the '100. Therefore, this rejection should be withdrawn.

Claims 1-17 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of U.S. Patent No. 6,201,072,; 1,117,949; 6004573(hereafter referred as "'072"; "'949"; and "'573")) in view of Shah. The applicant respectfully traverses because the subject matter of the present invention is patentably distinct from and they are not obvious modification of the subject matter disclosed in '072; '949 and '573 in view of Shah.

Although '072, '949 and '573 patents are related to biodegradable ABA-type block copolymers having reverse thermal gelation properties, there is no teaching or suggestion of a biodegradable polymeric system comprising a mixture of two triblock copolymers wherein an aqueous solution of said Component I triblock copolymer has a lower gelation temperature than an aqueous solution of said Component II triblock copolymer. The polymers of Shah are pH sensitive because they lose their thermal gelation properties in an environment with a pH value above 5.0. In contrast, the polymers of the present invention become gels at the proper temperature and maintain their gel status regardless of the pH value of the environment, and they don't gradually swell as the polymer erodes (Figure 4). In addition, since Shah's polymers respond to pH, which varies depending on the site of injection, they cannot form gels at a neutral pH. De-gelation in Shah occurs when the depot approaches normal body pH. Therefore, the polymers of the present invention are less dependent on the environment, while properties of the ionic system of Shah are dependent on where it is located. The gelation properties of the block copolymers of the present invention allow us to formulate them with compounds at a wide range of pH values, while Shah's system would only be applicable below a pH of 5 for which the system forms a gel. Therefore, use of Shah's system would not be feasible when the polymer is used to deliver a compound whose solubility requires a pH above 5. Therefore, the block copolymers of the present invention are patentably distinct from the polymers disclosed in Shah. Furthermore, no motivation is provided to blend various block copolymers to obtain a water

soluble triblock polymer mixture that is a liquid at lower temperatures and gels at higher physiological temperatures, even when the pH value is above 5, as claimed in the present invention. Therefore, the present claimed invention is not obvious modification of the subject matter disclosed in '072; '949 and '573 in view of Shah and the obvious type double patenting rejection should be withdrawn.

CONCLUSION

In light of the above, the Applicant respectfully submits that pending claims 1-23 are now in condition for allowance. Therefore, Applicant requests that the rejections and objections be withdrawn, and that the claims be allowed and passed to issue. If any impediment to the allowance of these claims remains after entry of this Amendment, the Examiner is strongly encouraged to call Dr. Weili Cheng or, in her absence, M. Wayne Western at (801) 566-6633 so that such matters may be resolved as expeditiously as possible.

The Commissioner is hereby authorized to charge any additional fee or to credit any overpayment in connection with this Amendment to Deposit Account No. 20-0100.

DATED this 31st day of August, 2005.

Respectfully submitted,

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